REMARKS

Applicants respectfully request entry of the amendment and reconsideration of the claims. Claims 62, 88, and 105 have been canceled without prejudice. Claims 80, 85, 93, 94, and 100 have been amended to further clarify the claimed invention. Claims 106-108 are new. After entry of the amendment, claims 58, 80-87, 89-90, 94-104, and 106-108 will be pending.

Applicants submit the amendment does not raise any issues of new matter and is supported by the specification.

Claim informalities

The Examiner objected to informalities in claims 85, 94, and 100. The claims have been amended as suggested by the Examiner. Withdrawal of the objection is respectfully requested.

Enablement

Claims 62, 80-90, and 94-105 were rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement. Applicants respectfully traverse this rejection.

Claims 62, 88, and 105 have been canceled without prejudice. Applicants do not acquiesce to the rejection of these claims under 35 U.S.C. § 112, first paragraph, and reserve the right to pursue the canceled subject matter in a continuation application. The rejection is discussed insofar as it applies to claims 80-87, 89-90, and 94-104.

The Examiner acknowledges the specification enables antagonist antibodies or antibody fragments that specifically bind a polypeptide comprising an amino acid sequence of SEQ ID NO:2; antagonist antibodies produced from hybridoma cells having ATCC accession number PTA-4119, PTA-4120, PTA-4121, or PTA-4122; a composition comprising said antibody or antibody fragments; and a kit comprising said antibodies or antibody fragments. The antibodies or antibody fragments can be humanized. The antibody fragments can be Fab, Fab', F(ab)'2, or Fv fragments.

The Examiner alleges the specification does not enable antibodies or antibody fragments that bind a polypeptide comprising amino acids 20-105 of SEQ ID NO:2. Applicants submit this rejection is moot in view of amended claim 80, which requires the claimed antagonist to specifically bind residues 20-105 of SEQ ID NO:2.

The Examiner alleges the specification lacks *in vivo* working examples demonstrating that the claimed antibodies or antibody fragments are effective for treating disease such as diabetes, infertility, polycystic ovary syndrome, or cancer and that recent failures in clinical trials using a VEGF antagonist indicate the unpredictability of angiogenesis inhibitors for cancer treatment. As a preliminary matter, Applicants note the claims currently under examination are drawn to antibodies that bind EG-VEGF and not methods of treating diabetes, infertility, polycystic ovary syndrome, or cancer with anti-EG-VEGF antibodies. Also, in contrast to the Examiner's opinions regarding VEGF antagonists, the VEGF antagonist antibody bevazimuab has been approved by the FDA for the treatment of cancer (see enclosed press release).

The Examiner alleges the specification does not teach any antibody fragments that are produced by the disclosed hybridomas. Applicants have amended the claims to clarify that the antibody fragment is a fragment of a monoclonal antibody produced by the disclosed hybridomas.

In view of the forgoing, Applicants submit the specification and knowledge in the art provides sufficient enabling disclosure to make and use the invention as claimed. Withdrawal of the enablement rejection is respectfully requested.

Written Description

Claims 62, 80-90, and 94-105 were rejected under 35 U.S.C. § 112, first paragraph, as lacking written description. Applicants submit the rejection is moot in view of amended claim 80, which requires the claimed antagonist to specifically bind residues 20-105 of SEQ ID NO:2. The specification provides sufficient written description of the claimed invention.

Claims 62, 88, and 105 have been canceled without prejudice. Applicants do not acquiesce to the rejection of these claims under 35 U.S.C. § 112, first paragraph, and reserve the right to pursue the canceled subject matter in a continuation application.

Withdrawal of the rejection is respectfully requested.

New Matter

Claims 62, 80-84, 88-90, and 105 were rejected under 35 U.S.C. § 112, first paragraph, as containing new matter. The Examiner's rejection is unclear. Without acquiescing to this

rejection, Applicants submit the rejection is moot in view of amended claim 80 that requires the claimed antagonist to specifically bind residues 20-105 of SEQ ID NO:2.

Claims 62, 88, and 105 have been canceled without prejudice. Applicants do not acquiesce to the rejection of these claims under 35 U.S.C. § 112, first paragraph, and reserve the right to pursue the canceled subject matter in a continuation application.

Withdrawal of the rejection is respectfully requested.

Anticipation

Claims 62, 80-84, 86-90, 94-99, and 101-105 were rejected under 35 U.S.C. § 102(e) as anticipated by U.S. Patent No. 6,485,938 (hereinafter the '938 patent), which claims priority to provisional application 60/165,905, filed on November 16, 1999. Applicants respectfully traverse this rejection.

Claims 62, 88, and 105 have been canceled without prejudice. Applicants do not acquiesce to the rejection of these claims under 35 U.S.C. § 102(e), and reserve the right to pursue the canceled subject matter in a continuation application. The rejection is discussed insofar as it applies to claims 80-84, 86-87, 89-90, 94-99, and 101-104.

The Examiner alleges the priority date of the rejected claims is September 7, 2000, the filing date of provisional application 60/230,978. Applicants respectfully disagree.

As noted by the Examiner, the present application claims priority to a number of patent applications including provisional application 60/145,698 (hereinafter the '698 application), filed on July 26, 1999. The filing date of at least the '698 application (July 26, 1999) predates the earliest priority date of the '938 patent. In the '698 application EG-VEGF (SEQ ID NO:2) is referred to as PRO1186 (SEQ ID NO:165). The '698 application describes the amino acid and nucleotide sequence for EG-VEGF (see for example pages 278-279 and Figures 65 and 66), discloses that amino acids 1-19 of SEQ ID NO:2 comprise a signal sequence (page 279, lines 4-5), demonstrates that EG-VEGF induces proliferation of ACE cells (see for example pages 280-281), and describes antagonist antibodies that bind EG-VEGF (see for example pages 18-19 and 208-215). The cited pages and figures are attached for the Examiner's convenience.

In view of the forgoing, Applicants submit the '938 patent does not anticipate any of the claims. The filing date of the '698 application (July 26, 1999) predates the earliest priority date of the '938 patent. Accordingly, withdrawal of the rejection is respectfully requested.

Conclusion

In view of the above amendments and remarks, Applicant respectfully requests a Notice of Allowance.

Applicants request an in person interview with the Examiner and the Examiner's supervisor. Applicants will contact the Examiner shortly to discuss a convenient date for the interview. The Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

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Date: September 6, 2005

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23552
PATENT TRADEMARK OFFICE

Thursday, Feb 26, 2004

FDA Approves Avastin, A Targeted Therapy for First-Line Metastatic Colorectal Cancer Patients

SOUTH SAN FRANCISCO, Calif. -- February 26, 2004 -- Genentech, Inc. (NYSE: DNA) announced today that the U.S. Food and Drug Administration (FDA) has approved Avastin™ (bevacizumab) to be used in combination with intravenous 5-Fluorouracil-based chemotherapy as a treatment for patients with first-line-or previously untreated-metastatic cancer of the colon or rectum. Avastin is the first FDA-approved therapy designed to inhibit angiogenesis, the process by which new blood vessels develop, which is necessary to support tumor growth and metastasis. Genentech will begin shipping Avastin within three calendar days.

The Avastin FDA approval is based on data from two trials. The pivotal trial was a large, placebo-controlled, randomized study that demonstrated a prolongation in the median survival of patients treated with Avastin plus the IFL (5-FU/Leucovorin/CPT-11) chemotherapy regimen by approximately five months, compared to patients treated with the IFL chemotherapy regimen alone (20.3 months versus 15.6 months). In addition, this study demonstrated an improvement in progression-free survival (PFS) of more than four months (10.6 months in the Avastin/IFL arm compared to 6.4 months in the IFL-alone arm). The survival and PFS results observed when Avastin is added to first-line chemotherapy are the longest ever reported in a randomized, Phase III study of patients with metastatic colorectal cancer.

In the pivotal trial, the most serious adverse events that occurred with Avastin included gastrointestinal perforations and wound healing complications, which were uncommon. The most common severe adverse events in this trial included hypertension, which was managed with oral medications, nosebleeds and asymptomatic proteinuria. Adverse events observed in other trials with Avastin included hemorrhage, congestive heart failure and thromboembolism.

"Today marks an important shift in the treatment of metastatic colorectal cancer, with the approval of an innovative treatment based on elegant science that targets cancer in an entirely new way," said Arthur D. Levinson, Ph.D., Genentech's chairman and chief executive officer. "The FDA's approval of Avastin would not have been possible without the dedication and passion of hundreds of

Genentech employees, clinical trial investigators, patient advocates, the FDA and, most importantly, all of the colorectal cancer patients and their families who volunteered for Avastin clinical trials. We're pleased that patients diagnosed with metastatic colorectal cancer today have a new treatment option."

"When I was diagnosed with Stage Four colorectal cancer, my first thought was of my family and whether there were any treatments that could help me," said Earl Woodard, a commercial airline pilot from Carthage, N.C. "I received Avastin in the Phase III clinical trial. I am not only excited to have benefited from Avastin and chemotherapy, but it is also a great feeling to have participated in a clinical trial that has led to a new drug being approved for patients with metastatic colorectal cancer."

About the Avastin Filing

The Avastin filing was submitted under the FDA's Fast Track program, which permits submission of documents on an ongoing-or "rolling"-basis to facilitate the review process. Genentech submitted the final documents for the Avastin Biologics License Application (BLA), which contained data from more than 1,400 patients who received treatment with Avastin in clinical trials, in September 2003. In November 2003, the FDA granted Priority Review status for Avastin and committed to reviewing the submission within six months of filing.

"Every nine minutes someone in the United States dies of colorectal cancer. As a patient advocate, I understand the desperate need for new therapies for patients with this disease," said Kevin Lewis, board chairperson of the Colon Cancer Alliance.

About the Avastin Pivotal Trial

The Avastin pivotal trial enrolled 925 patients with first-line (previously untreated) metastatic colorectal cancer, which is cancer that has spread beyond the colon or rectum. This trial was designed with a primary endpoint of survival and compared survival of patients treated with Avastin plus the IFL chemotherapy regimen to those treated with IFL chemotherapy and placebo. In addition to showing an improvement in survival in all patient populations studied, the trial also met its secondary endpoints by improving progression-free survival, response rate and duration of response.

About VEGF and Tumor Angiogenesis

The link between angiogenesis and cancer growth has been discussed by many researchers for decades. It wasn't until 1989 that a key growth factor influencing the process, Vascular Endothelial Growth Factor (VEGF), was discovered by Napoleone Ferrara, M.D., a staff scientist at Genentech. Dr. Ferrara and his team cloned VEGF, providing some of the first evidence that a specific angiogenic growth factor existed. This research was published in the journal Science in 1989. Dr. Ferrara then created a mouse antibody to this

protein. In 1993, Dr. Ferrara and his team at Genentech, in a study published in Nature, demonstrated that the antibody directed against VEGF could suppress angiogenesis and tumor growth in preclinical models, providing compelling evidence that VEGF can play a critical role in tumor growth. Clinical studies with a humanized version of the antibody, Avastin, began in 1997.

"Since the pivotal trial results were presented last year, I have had the privilege of meeting several patients who have received treatment with Avastin, and this has been the most rewarding part of watching a scientific theory progress from the lab to the clinic," said Dr. Ferrara. "The approval of Avastin is a testament to the many scientists both within Genentech and around the world who have worked tirelessly, even in the face of adversity and skepticism, to contribute to our understanding of angiogenesis and VEGF."

"Dr. Ferrara's scientific accomplishments and the approval of Avastin mark a turning point in science as it proves the long-pursued angiogenic hypothesis and, through an elegantly designed clinical trial, has turned a theory into a treatment for metastatic colorectal cancer patients," said Judah Folkman, M.D., professor of pediatric surgery at Children's Hospital and Harvard Medical School.

About Avastin

Avastin is a therapeutic antibody designed to inhibit VEGF, a protein that plays an important role in tumor angiogenesis and maintenance of existing tumor vessels. By inhibiting VEGF, Avastin is designed to interfere with the blood supply to a tumor, a process that is critical to a tumor's growth and metastasis. For full prescribing information and boxed warnings on Avastin and information about angiogenesis, visit http://www.gene.com. For more information on Avastin, visit www.avastin.com.

Based on data showing that VEGF may play a broad role in a range of cancers, Genentech is pursuing a late-stage clinical development program with Avastin evaluating its potential use in metastatic colorectal, renal cell (kidney), breast and non-small cell lung cancers. Avastin is also being evaluated in earlier stage trials as a potential therapy in prostate, ovarian, melanoma and several types of solid tumor cancers and hematologic malignancies.

About Colorectal Cancer

According to the American Cancer Society, more than 150 patients die every day from colorectal cancer in the United States. Colorectal cancer is the second leading cause of cancer death in the United States, the third most frequently diagnosed cancer, and approximately 147,000 new cases of colorectal cancer will be diagnosed in the United States in 2004.

About Genentech BioOncology

Genentech is committed to fundamentally changing the way cancer is

treated by establishing a broad oncology portfolio of innovative, targeted therapies that can improve patients' lives. Led by Rituxan® (Rituximab) and Herceptin® (Trastuzumab), the first two therapeutic antibodies approved to treat cancer in the United States and Avastin™ (bevacizumab), the first anti-angiogenic therapy approved to treat cancer in the United States, the BioOncology portfolio includes marketed and pipeline products in clinical trials for the seven most common lethal cancers.

Genentech has a robust pipeline of potential oncology therapies, including a small molecule designed to target the human epidermal growth factor receptor (HER1) pathway (also known as EGFR) and a therapeutic antibody directed at the HER pathway. To broaden Genentech's portfolio of targeted cancer therapies, research programs are leveraging Genentech's expertise in targeting additional components of the HER and angiogenesis pathways, as well as pathways that instruct cancer cells to die (i.e., apoptosis), and B-cell oncology.

About Genentech

Genentech is a leading biotechnology company that discovers, develops, manufactures and commercializes biotherapeutics for significant unmet medical needs. Eighteen of the currently approved biotechnology products originated from or are based on Genentech science. Genentech manufactures and commercializes 13 biotechnology products in the United States. The company has headquarters in South San Francisco, California and is traded on the New York Stock Exchange under the symbol DNA. For additional information about the company, please visit http://www.gene.com.

Genentech will be offering a live webcast of a discussion by Genentech management on Thursday, February 26, 2004 at 3:00 p.m. PT. The live webcast may be accessed on Genentech's website at http://www.gene.com. An archive of this webcast will be available until 5:00 p.m. PT on March 4, 2004. An audio replay of the webcast will be available beginning at 6:00 p.m. PT on February 26, 2004, through 5:00 p.m. PT on March 4, 2004. Access numbers for this replay are: 1-800-642-1687 (US/Canada) and 1-706-645-9291 (international); conference identification number is 5855709.

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For full prescribing information for Avastin, please call 650-225-7739 or visit http://www.gene.com.

(b) measuring the proliferation of the cells to determine if the test compound is an effective antagonist.

In another embodiment, the invention provides a method for identifying a compound that inhibits the expression of a PRO172, PRO175, PRO178, PRO188, PRO356, PRO179, PRO197, PRO198, PRO182, PRO195, PRO200, PRO211, PRO217, PRO219, PRO221, PRO224, PRO228, PRO245, PRO246, PRO258, PRO261, PRO272, PRO301, PRO322, PRO328, PRO331, PRO364, PRO366, PRO535, PRO819, PRO826, PRO1160, PRO1186 or PRO1246 polypeptide in cells that normally expresses the polypeptide, wherein the method comprises contacting the cells with a test compound and determining whether the expression of the PRO172, PRO175, PRO178, PRO188, PRO356, PRO179, PRO197, PRO198, PRO182, PRO195, PRO200, PRO211, PRO217, PRO219, PRO221, PRO224, PRO228, PRO245, PRO246, PRO258, PRO261, PRO272, PRO301, PRO322, PRO328, PRO331, PRO364, PRO366, PRO535, PRO819, PRO826, PRO1160, PRO1186 or PRO1246 polypeptide is inhibited. In a preferred aspect, this method comprises the steps of:

(a) contacting cells and a test compound to be screened under conditions suitable for allowing expression of the PRO172, PRO175, PRO178, PRO188, PRO356, PRO179, PRO197, PRO198, PRO182, PRO195, PRO200, PRO211, PRO217, PRO219, PRO221, PRO224, PRO228, PRO245, PRO246, PRO258, PRO261, PRO272, PRO301, PRO322, PRO328, PRO331, PRO364, PRO366, PRO535, PRO819, PRO826, PRO1160, PRO1186 or PRO1246 polypeptide; and

(b) determining the inhibition of expression of said polypeptide.

In a still further embodiment, the invention provides a compound that inhibits the expression of a PRO172, PRO175, PRO178, PRO188, PRO356, PRO179, PRO197, PRO198, PRO182, PRO195, PRO200, PRO211, PRO217, PRO219, PRO221, PRO224, PRO228, PRO245, PRO246, PRO258, PRO261, PRO272, PRO301, PRO322, PRO328, PRO331, PRO364, PRO366, PRO535, PRO819, PRO826, PRO1160, PRO1186 or PRO1246 polypeptide, such as a compound that is identified by the methods set forth above.

Another aspect of the present invention is directed to an agonist or an antagonist of a PRO172, PRO175, PRO178, PRO188, PRO356, PRO179, PRO197, PRO198, PRO182, PRO195, PRO200, PRO211, PRO217, PRO219, PRO221, PRO224, PRO228, PRO245, PRO246, PRO258, PRO261, PRO272, PRO301, PRO322, PRO328, PRO331, PRO364,

PRO366, PRO535, PRO819, PRO826, PRO1160, PRO1186 or PRO1246 polypeptide which may optionally be identified by the methods described above.

One type of antagonist of a PRO172, PRO175, PRO178, PRO188, PRO356, PRO179, PRO197, PRO198, PRO182, PRO195, PRO200, PRO211, PRO217, PRO219, PRO221, PRO224, PRO228, PRO245, PRO246, PRO258, PRO261, PRO272, PRO301, PRO322, PRO328, PRO331, PRO364, PRO366, PRO535, PRO819, PRO826, PRO1160, PRO1186 or PRO1246 polypeptide that inhibit one or more of the functions or activities of the PRO172, PRO175, PRO178, PRO188, PRO356, PRO179, PRO197, PRO198, PRO182, PRO195, PRO200, PRO211, PRO217, PRO219, PRO221, PRO224, PRO228, PRO245, PRO246, PRO258, PRO261, PRO272, PRO301, PRO322, PRO328, PRO331, PRO364, PRO366, PRO535, PRO819, PRO826, PRO1160, PRO1186 or PRO1246 polypeptide is an antibody. Hence, in another aspect, the invention provides an isolated antibody that binds a PRO172, PRO175, PRO178, PRO188, PRO356, PRO179, PRO197, PRO198, PRO182, PRO195, PRO200, PRO211, PRO217, PRO219, PRO221, PRO224, PRO228, PRO245, PRO246, PRO258, PRO261, PRO272, PRO301, PRO322, PRO328, PRO331, PRO364, PRO366, PRO535, PRO819, PRO826, PRO1160, PRO1186 or PRO1246 polypeptide. In a preferred aspect, the antibody is a monoclonal antibody, which preferably has non-human complementarity-determining-region (CDR) residues and human framework-region (FR) residues. The antibody may be labeled and may be immobilized on a solid support. In a further aspect, the antibody is an antibody fragment, a single-chain antibody, or an anti-idiotypic antibody. Preferably, the antibody specifically binds to the polypeptide.

In a still further aspect, the present invention provides a method for diagnosing a disease or susceptibility to a disease which is related to a mutation in a PRO172, PRO175, PRO178, PRO188, PRO356, PRO179, PRO197, PRO198, PRO182, PRO195, PRO200, PRO211, PRO217, PRO219, PRO221, PRO224, PRO228, PRO245, PRO246, PRO258, PRO261, PRO272, PRO301, PRO322, PRO328, PRO331, PRO364, PRO366, PRO535, PRO819, PRO826, PRO1160, PRO1186 or PRO1246 polypeptide-encoding nucleic acid sequence comprising:

(a) isolating a nucleic acid sequence encoding a PRO172, PRO175, PRO178, PRO188, PRO356, PRO179, PRO197, PRO198, PRO182, PRO195, PRO200, PRO211, PRO217, PRO219, PRO221, PRO224, PRO228, PRO245, PRO246, PRO258, PRO261, PRO272,

C. Antibodies

Some of the most promising drug candidates according to the present invention are antibodies and antibody fragments that may inhibit the production or the gene product of the genes identified herein and/or reduce the activity of the gene products.

i. Polyclonal Antibodies

Methods of preparing polyclonal antibodies are known to the skilled artisan. Polyclonal antibodies can be raised in a mammal, for example, by one or more injections of an immunizing agent and, if desired, an adjuvant. Typically, the immunizing agent and/or adjuvant will be injected in the mammal by multiple subcutaneous or intraperitoneal injections. The immunizing agent may include the PRO172, PRO175, PRO178, PRO188, PRO356, PRO179, PRO197, PRO198, PRO182, PRO195, PRO200, PRO211, PRO217, PRO219, PRO221, PRO224, PRO228, PRO245, PRO246, PRO258, PRO261, PRO272, PRO301, PRO322, PRO328, PRO331, PRO364, PRO366, PRO535, PRO819, PRO826, PRO1160, PRO1186 or PRO1246 polypeptide or a fusion protein thereof. It may be useful to conjugate the immunizing agent to a protein known to be immunogenic in the mammal being immunized. Examples of such immunogenic proteins include, but are not limited to, keyhole limpet hemocyanin, serum albumin, bovine thyroglobulin, and soybean trypsin inhibitor. Examples of adjuvants that may be employed include Freund's complete adjuvant and MPL-TDM adjuvant (monophosphoryl Lipid A or synthetic trehalose dicorynomycolate). The immunization protocol may be selected by one skilled in the art without undue experimentation.

ii. Monoclonal Antibodies

The anti-PRO172, anti-PRO175, anti-PRO178, anti-PRO188, anti-PRO356, anti-PRO179, anti-PRO197, anti-PRO198, anti-PRO182, anti-PRO195, anti-PRO200, anti-PRO211, anti-PRO217, anti-PRO219, anti-PRO221, anti-PRO224, anti-PRO228, anti-PRO245, anti-PRO246, anti-PRO258, anti-PRO261, anti-PRO272, anti-PRO301, anti-PRO322, anti-PRO328, anti-PRO331, anti-PRO364, anti-PRO366, anti-PRO535, anti-PRO819, anti-PRO826, anti-PRO1160, anti-PRO1186 or anti-PRO1246 antibodies may, alternatively, be monoclonal antibodies. Monoclonal antibodies may be prepared using hybridoma methods, such as those described by Kohler and Milstein, Nature, 256:495 (1975). In a hybridoma method, a mouse, hamster, or

other appropriate host animal is typically immunized with an immunizing agent to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the immunizing agent. Alternatively, the lymphocytes may be immunized *in vitro*.

The immunizing agent will typically include the PRO172, PRO175, PRO178, PRO188, PRO356, PRO179, PRO197, PRO198, PRO182, PRO195, PRO200, PRO211, PRO217, PRO219, PRO221, PRO224, PRO228, PRO245, PRO246, PRO258, PRO261, PRO272, PRO301, PRO322, PRO328, PRO331, PRO364, PRO366, PRO535, PRO819, PRO826, PRO1160, PRO1186 or PRO1246 polypeptide or a fusion protein thereof. Generally, either peripheral blood lymphocytes ("PBLs") are used if cells of human origin are desired, or spleen cells or lymph node cells are used if non-human mammalian sources are desired. The lymphocytes are then fused with an immortalized cell line using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell. Goding, Monoclonal Antibodies: Principles and Practice (New York: Academic Press, 1986), pp. 59-103. Immortalized cell lines are usually transformed mammalian cells, particularly myeloma cells of rodent, bovine, and human origin. Usually, rat or mouse myeloma cell lines are employed. The hybridoma cells may be cultured in a suitable culture medium that preferably contains one or more substances that inhibit the growth or survival of the unfused, immortalized cells. For example, if the parental cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine ("HAT medium"), which substances prevent the growth of HGPRT-deficient cells.

Preferred immortalized cell lines are those that fuse efficiently, support stable high-level expression of antibody by the selected antibody-producing cells, and are sensitive to a medium such as HAT medium. More preferred immortalized cell lines are murine myeloma lines, which can be obtained, for instance, from the Salk Institute Cell Distribution Center, San Diego, California and the American Type Culture Collection, Manassas, Virginia. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies. Kozbor, J. Immunol., 133:3001 (1984); Brodeur *et al.*, Monoclonal Antibody Production Techniques and Applications (Marcel Dekker, Inc.: New York, 1987) pp. 51-63.

The culture medium in which the hybridoma cells are cultured can then be assayed for the presence of monoclonal antibodies directed against PRO172, PRO175, PRO178, PRO188,

PRO356, PRO179, PRO197, PRO198, PRO182, PRO195, PRO200, PRO211, PRO217, PRO219, PRO221, PRO224, PRO228, PRO245, PRO246, PRO258, PRO261, PRO272, PRO301, PRO322, PRO328, PRO331, PRO364, PRO366, PRO535, PRO819, PRO826, PRO1160, PRO1186 or PRO1246. Preferably, the binding specificity of monoclonal antibodies produced by the hybridoma cells is determined by immunoprecipitation or by an *in vitro* binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunoabsorbent assay (ELISA). Such techniques and assays are known in the art. The binding affinity of the monoclonal antibody can, for example, be determined by the Scatchard analysis of Munson and Pollard, Anal. Biochem., 107:220 (1980).

After the desired hybridoma cells are identified, the clones may be subcloned by limiting dilution procedures and grown by standard methods. Goding, *supra*. Suitable culture media for this purpose include, for example, Dulbecco's Modified Eagle's Medium and RPMI-1640 medium. Alternatively, the hybridoma cells may be grown *in vivo* as ascites in a mammal.

The monoclonal antibodies secreted by the subclones may be isolated or purified from the culture medium or ascites fluid by conventional immunoglobulin purification procedures such as, for example, protein A-Sepharose, hydroxylapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography.

The monoclonal antibodies may also be made by recombinant DNA methods, such as those described in U.S. Patent No. 4,816,567. DNA encoding the monoclonal antibodies of the invention can be readily isolated and sequenced using conventional procedures (*e.g.*, by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of murine antibodies). The hybridoma cells of the invention serve as a preferred source of such DNA. Once isolated, the DNA may be placed into expression vectors, which are then transfected into host cells such as simian COS cells, Chinese hamster ovary (CHO) cells, or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. The DNA also may be modified, for example, by substituting the coding sequence for human heavy- and light-chain constant domains in place of the homologous murine sequences (U.S. Patent No. 4,816,567; Morrison *et al.*, *supra*) or by covalently joining to the immunoglobulin coding sequence all or part of the coding sequence for a non-immunoglobulin polypeptide. Such a non-immunoglobulin polypeptide can be substituted for the constant domains of an antibody of the invention, or can be substituted for

the variable domains of one antigen-combining site of an antibody of the invention to create a chimeric bivalent antibody.

The antibodies may be monovalent antibodies. Methods for preparing monovalent antibodies are well known in the art. For example, one method involves recombinant expression of immunoglobulin light chain and modified heavy chain. The heavy chain is truncated generally at any point in the Fc region so as to prevent heavy-chain crosslinking. Alternatively, the relevant cysteine residues are substituted with another amino acid residue or are deleted so as to prevent crosslinking.

In vitro methods are also suitable for preparing monovalent antibodies. Digestion of antibodies to produce fragments thereof, particularly Fab fragments, can be accomplished using routine techniques known in the art.

iii. Human and Humanized Antibodies

The anti-PRO172, anti-PRO175, anti-PRO178, anti-PRO188, anti-PRO356, anti-PRO179, anti-PRO197, anti-PRO198, anti-PRO182, anti-PRO195, anti-PRO200, anti-PRO211, anti-PRO217, anti-PRO219, anti-PRO221, anti-PRO224, anti-PRO228, anti-PRO245, anti-PRO246, anti-PRO258, anti-PRO261, anti-PRO272, anti-PRO301, anti-PRO322, anti-PRO328, anti-PRO331, anti-PRO364, anti-PRO366, anti-PRO535, anti-PRO819, anti-PRO826, anti-PRO1160, anti-PRO1186 or anti-PRO1246 antibodies may further comprise humanized antibodies or human antibodies. Humanized forms of non-human (*e.g.*, murine) antibodies are chimeric immunoglobulins, immunoglobulin chains, or fragments thereof (such as Fv, Fab, Fab', $F(ab')_2$ or other antigen-binding subsequences of antibodies) that contain minimal sequence derived from non-human immunoglobulin. Humanized antibodies include human immunoglobulins (recipient antibody) in which residues from a CDR of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat, or rabbit having the desired specificity, affinity, and capacity. In some instances, Fv framework residues of the human immunoglobulin are replaced by corresponding non-human residues. Humanized antibodies may also comprise residues that are found neither in the recipient antibody nor in the imported CDR or framework sequences. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin, and all or substantially all of the

FR regions are those of a human immunoglobulin consensus sequence. The humanized antibody preferably also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. Jones *et al.*, Nature, 321: 522-525 (1986); Riechmann *et al.*, Nature, 332: 323-329 (1988); Presta, Curr. Op. Struct. Biol., 2:593-596 (1992).

Methods for humanizing non-human antibodies are well known in the art. Generally, a humanized antibody has one or more amino acid residues introduced into it from a source that is non-human. These non-human amino acid residues are often referred to as "import" residues, which are typically taken from an "import" variable domain. Humanization can be essentially performed following the method of Winter and co-workers (Jones *et al.*, Nature, 321: 522-525 (1986); Riechmann *et al.*, Nature, 332: 323-327 (1988); Verhoeyen *et al.*, Science, 239: 1534-1536 (1988)), by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. Accordingly, such "humanized" antibodies are chimeric antibodies (U.S. Patent No. 4,816,567), wherein substantially less than an intact human variable domain has been substituted by the corresponding sequence from a non-human species. In practice, humanized antibodies are typically human antibodies in which some CDR residues and possibly some FR residues are substituted by residues from analogous sites in rodent antibodies.

Human antibodies can also be produced using various techniques known in the art, including phage display libraries. Hoogenboom and Winter, J. Mol. Biol., 227: 381 (1991); Marks *et al.*, J. Mol. Biol., 222: 581 (1991). The techniques of Cole *et al.* and Boerner *et al.* are also available for the preparation of human monoclonal antibodies. Cole *et al.*, Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, p. 77 (1985) and Boerner *et al.*, J. Immunol., 147(1): 86-95 (1991). Similarly, human antibodies can be made by introducing human immunoglobulin loci into transgenic animals, *e.g.*, mice in which the endogenous immunoglobulin genes have been partially or completely inactivated. Upon challenge, human antibody production is observed that closely resembles that seen in humans in all respects, including gene rearrangement, assembly, and antibody repertoire. This approach is described, for example, in U.S. Patent Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; and 5,661,016, and in the following scientific publications: Marks *et al.*, Bio/Technology, 10: 779-783 (1992); Lonberg *et al.*, Nature, 368: 856-859 (1994); Morrison, Nature, 368: 812-813 (1994); Fishwild *et al.*, Nature Biotechnology, 14: 845-851 (1996); Neuberger, Nature Biotechnology, 14: 826 (1996); Lonberg and Huszar, Intern. Rev. Immunol., 13: 65-93 (1995).

iv. Bispecific Antibodies

Bispecific antibodies are monoclonal, preferably human or humanized, antibodies that have binding specificities for at least two different antigens. In the present case, one of the binding specificities is for the PRO172, PRO175, PRO178, PRO188, PRO356, PRO179, PRO197, PRO198, PRO182, PRO195, PRO200, PRO211, PRO217, PRO219, PRO221, PRO224, PRO228, PRO245, PRO246, PRO258, PRO261, PRO272, PRO301, PRO322, PRO328, PRO331, PRO364, PRO366, PRO535, PRO819, PRO826, PRO1160, PRO1186 or PRO1246 polypeptide, the other one is for any other antigen, and preferably for a cell-surface protein or receptor or receptor subunit.

Methods for making bispecific antibodies are known in the art. Traditionally, the recombinant production of bispecific antibodies is based on the co-expression of two immunoglobulin heavy-chain/light-chain pairs, where the two heavy chains have different specificities. Milstein and Cuello, Nature, 305: 537-539 (1983). Because of the random assortment of immunoglobulin heavy and light chains, these hybridomas (quadromas) produce a potential mixture of ten different antibody molecules, of which only one has the correct bispecific structure. The purification of the correct molecule is usually accomplished by affinity chromatography steps. Similar procedures are disclosed in WO 93/08829, published 13 May 1993, and in Traunecker *et al.*, EMBO J., 10: 3655-3659 (1991).

Antibody variable domains with the desired binding specificities (antibody-antigen combining sites) can be fused to immunoglobulin constant- domain sequences. The fusion preferably is with an immunoglobulin heavy-chain constant domain, comprising at least part of the hinge, CH2, and CH3 regions. It is preferred to have the first heavy-chain constant region (CH1) containing the site necessary for light-chain binding present in at least one of the fusions. DNAs encoding the immunoglobulin heavy-chain fusions and, if desired, the immunoglobulin light chain, are inserted into separate expression vectors, and are co-transfected into a suitable host organism. For further details of generating bispecific antibodies, see, for example, Suresh *et al.*, Methods in Enzymology, 121: 210 (1986).

v. Heteroconjugate Antibodies

Heteroconjugate antibodies are composed of two covalently joined antibodies. Such antibodies have, for example, been proposed to target immune-system cells to unwanted cells

(U.S. Patent No. 4,676,980), and for treatment of HIV infection. WO 91/00360; WO 92/200373; EP 03089. It is contemplated that the antibodies may be prepared *in vitro* using known methods in synthetic protein chemistry, including those involving crosslinking agents. For example, immunotoxins may be constructed using a disulfide-exchange reaction or by forming a thioether bond. Examples of suitable reagents for this purpose include iminothiolate and methyl-4-mercaptobutyrimidate and those disclosed, for example, in U.S. Patent No. 4,676,980.

vi. Effector Function Engineering

It may be desirable to modify the antibody of the invention with respect to effector function, so as to enhance, *e.g.*, the effectiveness of the antibody in treating cancer. For example, cysteine residue(s) may be introduced into the Fc region, thereby allowing interchain disulfide bond formation in this region. The homodimeric antibody thus generated may have improved internalization capability and/or increased complement-mediated cell killing and antibody-dependent cellular cytotoxicity (ADCC). See Caron *et al.*, J. Exp Med., 176: 1191-1195 (1992) and Shopes, J. Immunol., 148: 2918-2922 (1992). Homodimeric antibodies with enhanced anti-tumor activity may also be prepared using heterobifunctional cross-linkers as described in Wolff *et al.* Cancer Research, 53: 2560-2565 (1993). Alternatively, an antibody can be engineered that has dual Fc regions and may thereby have enhanced complement lysis and ADCC capabilities. See Stevenson *et al.*, Anti-Cancer Drug Design, 3: 219-230 (1989).

vii. Immunoconjugates

The invention also pertains to immunoconjugates comprising an antibody conjugated to a cytotoxic agent such as a chemotherapeutic agent, toxin (*e.g.*, an enzymatically active toxin of bacterial, fungal, plant, or animal origin, or fragments thereof), or a radioactive isotope (*i.e.*, a radioconjugate).

Chemotherapeutic agents useful in the generation of such immunoconjugates have been described above. Enzymatically active toxins and fragments thereof that can be used include diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from *Pseudomonas aeruginosa*), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, *Aleurites fordii* proteins, dianthin proteins, *Phytolaca americana* proteins (PAPI, PAPII, and PAP-S), momordica charantia inhibitor, curcin, crotin, sapaonaria officinulis inhibitor, gelonin,

mitogellin, restrictocin, phenomycin, enomycin, and the tricothecenes. A variety of radionuclides are available for the production of radioconjugated antibodies. Examples include ^{212}Bi, ^{131}I, ^{131}In, ^{90}Y, and ^{186}Re.

Conjugates of the antibody and cytotoxic agent are made using a variety of bifunctional protein-coupling agents such as N-succinimidyl-3-(2-pyridyldithiol) propionate (SPDP), iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCL), active esters (such as disuccinimidyl suberate), aldehydes (such as glutareldehyde), bis-azido compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as tolyene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in Vitetta *et al.*, Science, 238: 1098 (1987). Carbon-14-labeled 1-isothiocyanatobenzyl-3-methyldiethylene triaminepentaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of radionucleotide to the antibody. See WO94/11026.

In another embodiment, the antibody may be conjugated to a "receptor" (such streptavidin) for utilization in tumor pretargeting wherein the antibody-receptor conjugate is administered to the patient, followed by removal of unbound conjugate from the circulation using a clearing agent and then administration of a "ligand" (*e.g.*, avidin) that is conjugated to a cytotoxic agent (*e.g.*, a radionucleotide).

viii. Immunoliposomes

The antibodies disclosed herein may also be formulated as immunoliposomes. Liposomes containing the antibody are prepared by methods known in the art, such as described in Epstein *et al.*, Proc. Natl. Acad. Sci. USA, 82: 3688 (1985); Hwang *et al.*, Proc. Natl. Acad. Sci. USA, 77: 4030 (1980); and U.S. Pat. Nos. 4,485,045 and 4,544,545. Liposomes with enhanced circulation time are disclosed in U.S. Patent No. 5,013,556.

Particularly useful liposomes can be generated by the reverse-phase evaporation method with a lipid composition comprising phosphatidylcholine, cholesterol, and PEG-derivatized phosphatidylethanolamine (PEG-PE). Liposomes are extruded through filters of defined pore size to yield liposomes with the desired diameter. Fab' fragments of the antibody of the present invention can be conjugated to the liposomes as described in Martin *et al.*, J. Biol. Chem., 257:

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using the ALIGN-2 sequence alignment analysis of the full-length sequence shown in Figure 64 (SEQ ID NO:160) evidenced sequence identity of the PRO1160 amino acid sequence to the following Dayhoff sequences: B30305, GEN13490, I53641. S53363, HA34_BRELC, SP96_DICDI, S36326, SSU51197_10, MUC1_XENLA, TCU32448_1 and AF000409_1.

EXAMPLE 36

Isolation of cDNA clones encoding PRO1186

Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the Incyte database. This Incyte EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (*e.g.*, GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul *et al.*, Methods in Enzymology. 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases, 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56748.

In light of an observed sequence homology between the DNA56748 consensus sequence and an EST sequence no. 3476792 encompassed within a clone (from a library constructed from ovarian tissue) including this Incyte EST, identified from the Incyte database, the Incyte clone including Incyte EST no. 3476792 was purchased and the cDNA insert was obtained and sequenced. It was found herein that that insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 65 (SEQ ID NO:164) and is herein designated DNA60621-1516.

Clone DNA60621-1516 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 91-93 and ending at the stop codon at nucleotide positions 406-408 (Figure 65). The predicted polypeptide precursor is 105 amino acids long (Figure 66; SEQ ID NO:165). The full-length PRO1186 protein shown in Figure 66 has an estimated molecular weight of about 11,715 daltons and a pI of about 9.05.

Analysis of the full-length PRO1186 sequence shown in Figure 66 (SEQ ID NO:165) evidences the presence of an important polypeptide domain as shown in Figure 66, wherein the location given for that important polypeptide domain is approximate as described above. Analysis of the full-length PRO1186 sequence evidences the presence of a signal peptide from about amino acid 1 to about amino acid 19. Clone DNA60621-1516 was deposited with the ATCC on August 4, 1998, and is assigned ATCC deposit no. 203091.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using the ALIGN-2 sequence alignment analysis of the full-length sequence shown in Figure 66 (SEQ ID NO:165), evidenced sequence identity between the PRO1186 amino acid sequence and the following Dayhoff sequences: VPRA_DENPO, LFE4_CHICK, AF034208_1, AF030433_1, A55035, COL_RABIT, CELB0507_9, S67826_1, S34665 and CRU73817_1.

EXAMPLE 37

Isolation of cDNA clones encoding PRO1246

Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the Incyte database, designated Incyte EST cluster sequence no. 56853. This Incyte EST cluster sequence no. 56853 was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (*e.g.*, GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul *et al.*, Methods in Enzymology, 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases, 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56021.

In light of an observed sequence homology between the DNA56021 consensus sequence and an EST sequence encompassed within clone no. 2481345, from the Incyte database, clone no. 2481345 was purchased and the cDNA insert was obtained and sequenced. It was found herein that that insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figures 67A-B (SEQ ID NO:166) and is herein designated DNA64885-1529.

Clone DNA64885-1529 contains a single open reading frame with an apparent translational

initiation site at nucleotide positions 119-121 and ending at the stop codon at nucleotide positions 1727-1729 (Figures 67A-B). The predicted polypeptide precursor is 536 amino acids long (Figure 68; SEQ ID NO:167). The full-length PRO1246 protein shown in Figure 68 has an estimated molecular weight of about 61,450 daltons and a pI of about 9.17.

Analysis of the full-length PRO1246 sequence shown in Figure 68 (SEQ ID NO:167) evidences the presence of a variety of important polypeptide domains as shown in Figure 68, wherein the locations given for those important polypeptide domains are approximate as described above. Analysis of the full-length PRO1246 sequence evidences the presence of the following features: a signal peptide from amino acid 1 to about amino acid 15, a transmembrane domain from about amino acid 347 to about amino acid 365, potential N-glycosylation sites from about amino acid 108 to about amino acid 111, from about amino acid 166 to about amino acid 169, from about amino acid 193 to about amino acid 196, from about amino acid 262 to about amino acid 265, from about amino acid 375 to about amino acid 378, from about amino acid 413 to about amino acid 416, and from about amino acid 498 to about amino acid 501, and amino acid sequence blocks having homology to sulfatase proteins from about amino acid 286 to about amino acid 315, from about amino acid 359 to about amino acid 369 and from amino acid 78 to about amino acid 97. Clone DNA64885-1529 was deposited with the ATCC on November 3, 1998, and is assigned ATCC deposit no. 203457.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using the ALIGN-2 sequence alignment analysis of the full-length sequence shown in Figure 68 (SEQ ID NO:167) evidenced sequence identity between the PRO1246 amino acid sequence and the following Dayhoff sequences: P_R51355, CELK09C4_1, BCU44852_1, IDS_HUMAN, G65169, E64903, ARSA_HUMAN, GL6S_HUMAN, HSARSF_1 and GEN12648.

EXAMPLE 38

Stimulation of Endothelial Cell Proliferation

This assay is designed to determine whether PRO1186 shows the ability to stimulate adrenal cortical capillary endothelial cell (ACE) growth.

Bovine adrenal cortical capillary endothelial cells (ACE) (from primary culture, maximum of 12-14 passages) were plated in 96-well plates at 500 cells/well per 100 microliter. Assay media included low glucose DMEM, 10% calf serum, 2 mM glutamine, and 1X

penicillin/streptomycin/fungizone. Control wells included the following: (1) no ACE cells added; (2) ACE cells alone; (3) ACE cells plus VEGF (5 ng/ml); and (4) ACE cells plus FGF (5ng/ml). The control or test sample, (in 100 microliter volumes), was then added to the wells (at dilutions of 1%, 0.1% and 0.01%, respectively). The cell cultures were incubated for 6-7 days at 37°C/5% CO_2. After the incubation, the media in the wells was aspirated, and the cells were washed 1X with PBS. An acid phosphatase reaction mixture (100 microliter: 0.1M sodium acetate, pH 5.5, 0.1% Triton X-100, 10 mM p-nitrophenyl phosphate) was then added to each well. After a 2 hour incubation at 37°C, the reaction was stopped by addition of 10 microliters 1N NaOH. Optical density (OD) was measured on a microplate reader at 405 nm.

The activity of PRO1186 was calculated as the fold increase in proliferation (as determined by the acid phosphatase activity, OD 405 nm) relative to (1) cell only background, and (2) relative to maximum stimulation by VEGF. VEGF (at 3-10 ng/ml) and FGF (at 1-5 ng/ml) were employed as an activity reference for maximum stimulation. Results of the assay were considered "positive" if the observed stimulation was ≥ 50% increase over background.

PRO1186 assayed "positive" as follows:

1% dilution = 1.75 fold stimulation

0.1% dilution = 1.39 fold stimulation

0.01% dilution = 1.28 fold stimulation

Compared to VEGF (5 ng/ml) control:

1% dilution = 1.24 fold stimulation

Compared to FGB (5 ng/ml) control:

1% dilution = 1.46 fold stimulation

EXAMPLE 39

Inhibition of Vascular Endothelial Growth Factor (VEGF) Stimulated Proliferation of Endothelial Cell Growth

The ability of various PRO polypeptides to inhibit VEGF stimulated proliferation of endothelial cells was tested. Specifically, bovine adrenal cortical capillary endothelial cells (ACE) (from primary culture, maximum of 12-14 passages) were plated in 96-well plates at 500 cells/well per 100 microliter. Assay media included low glucose DMEM, 10% calf serum, 2 mM glutamine, and 1X penicillin/streptomycin/fungizone. Control wells included the following: (1)

FIGURE 65

TGGCCTCCCCAGCTTGCCAGGCACAAGGCTGAGCGGGAGGAAGCGAGAGGCATCTAAGCAGG
CAGTGTTTTGCCTTCACCCCAAGTGACCATGAGAGGTGCCACGCGAGTCTCAATCATGCTCC
TCCTAGTAACTGTGTCTGACTGTGCTGTGATCACAGGGGCCTGTGAGCGGGATGTCCAGTGT
GGGGCAGGCACCTGCTGTGCCATCAGCCTGTGGCTTCGAGGGCTGCGGATGTGCACCCCGCT
GGGGCGGGAAGGCGAGGAGTGCCACCCCGGCAGCCACAAGGTCCCCTTCTTCAGGAAACGCA
AGCACCACACCTGTCCTTGCTTGCCCAACCTGCTGTGCTCCAGGTTCCCGGACGGCAGGTAC
CGCTGCTCCATGGACTTGAAGAACATCAATTTTTAGGCGCTTGCCTGGTCTCAGGATACCCA
CCATCCTTTTCCTGAGCACAGCCTGGATTTTTATTTCTGCCATGAAACCCAGCTCCCATGAC
TCTCCCAGTCCCTACACTGACTACCCTGATCTCTCTTGTCTAGTACGCACATATGCACACAG
GCAGACATACCTCCCATCATGACATGGTCCCCAGGCTGGCCTGAGGATGTCACAGCTTGAGG
CTGTGGTGTGAAAGGTGGCCAGCCTGGTTCTCTTCCCTGCTCAGGCTGCCAGAGAGGTGGTA
AATGGCAGAAAGGACATTCCCCCTCCCCTCCCCAGGTGACCTGCTCTCTTTCCTGGGCCCTG
CCCCTCTCCCCACATGTATCCCTCGGTCTGAATTAGACATTCCTGGGCACAGGCTCTTGGGT
GCATTGCTCAGAGTCCCAGGTCCTGGCCTGACCCTCAGGCCCTTCACGTGAGGTCTGTGAGG
ACCAATTTGTGGGTAGTTCATCTTCCCTCGATTGGTTAACTCCTTAGTTTCAGACCACAGAC
TCAAGATTGGCTCTTCCCAGAGGGCAGCAGACAGTCACCCCAAGGCAGGTGTAGGGAGCCCA
GGGAGGCCAATCAGCCCCCTGAAGACTCTGGTCCCAGTCAGCCTGTGGCTTGTGGCCTGTGA
CCTGTGACCTTCTGCCAGAATTGTCATGCCTCTGAGGCCCCCTCTTACCACACTTTACCAGT
TAACCACTGAAGCCCCCAATTCCCACAGCTTTTCCATTAAAATGCAAATGGTGGTGGTTCAA
TCTAATCTGATATTGACATATTAGAAGGCAATTAGGGTGTTTCCTTAAACAACTCCTTTCCA
AGGATCAGCCCTGAGAGCAGGTTGGTGACTTTGAGGAGGGCAGTCCTCTGTCCAGATTGGGG
TGGGAGCAAGGGACAGGGAGCAGGGCAGGGGCTGAAAGGGGCACTGATTCAGACCAGGGAGG
CAACTACACACCAACATGCTGGCTTTAGAATAAAAGCACCAACTGAAAAAA

FIGURE 66

Signal peptide: Amino acids 1-19

MRGATRVSIMLLLVTVSDCAVITGACERDVQCGAGTCCAISLWLRGLRMCTPLGREGEECHP
GSHKVPFFRKRKHHTCPCLPNLLCSRFPDGRYRCSMDLKNINF